

# TUBERCULOSIS

## TB

### ✓ DISEASE AND EPIDEMIOLOGY

#### **Clinical Description:**

When unexposed persons inhale TB organisms (tubercle bacilli) into their lungs, the organisms travel to the lung's alveoli, where the organisms are ingested by macrophages (a type of white blood cell). Infection begins with the multiplication of tubercle bacilli within the macrophages.

#### **Latent infection (LTBI):**

In most cases, the immune system contains the organism and prevents the development of disease. LTBI refers to individuals who are infected, but asymptomatic and not infectious. They will have a positive reaction to either the tuberculin skin test or an FDA approved in-vitro serologic test.

Currently, QuantiFERON –TB Gold is the only FDA approved in-vitro serologic test available in the United States. This test detects the release of interferon-gamma in fresh heparinized whole blood from sensitized persons when it is incubated with mixtures of synthetic peptides representing two proteins present in *M. tuberculosis*. The Centers for Disease Control and Prevention recommends that QuantiFERON –TB Gold may be used in all circumstances in which the tubercular skin test or TST is currently used, including contact investigations, evaluation of recent immigrants, and sequential-testing surveillance programs for infection control.

Chest radiographs may be used to rule out the possibility of pulmonary tuberculosis in a person who has a positive reaction to either the tuberculin skin test or an FDA approved in-vitro serologic test and no symptoms of disease.

As long as the immune system remains vigorous, TB stays dormant, walled up in small structures created by the immune system (granuloma). However, individuals with LTBI remain at risk of developing active TB disease throughout their lifetime.

#### **TB disease:**

Active TB is an infectious disease that occurs when these dormant or latent TB organisms begin to multiply in a person.

Symptoms of TB disease include fever, fatigue, weight loss, and night sweats. TB can affect any part of the body, but usually affects the lungs (where it is called pulmonary TB).

**Pulmonary TB:** Signs and symptoms specific to pulmonary TB include cough (progressing from nonproductive to productive); in advanced

stages, blood-tinged sputum (hemoptysis); and an abnormal chest radiograph, progressing from infiltrates to open cavities as the disease progresses untreated.

**Extra-pulmonary TB:** Typical extrapulmonary manifestations of TB include hepatic, meningitis, pericarditis, skeletal, genitourinary, gastrointestinal, lymphadenitis, cutaneous, and other miscellaneous sites.

About 10% of infected people will develop active tuberculosis at some time in their life. The risk is considerably higher for persons who are aged or immunosuppressed, especially those with HIV infection.

### **Causative Agent:**

TB is caused by bacteria (tubercle bacilli) that make up the *Mycobacterium tuberculosis* complex. There are five closely related organisms in the complex: *M. tuberculosis* (*M. tb*), *M. bovis*, *M. africanum*, *M. microti* and *M. canetti*. *M. tuberculosis* and *bovis* cause human disease in the U.S., *M. africanum* and *canetti* are rare causes of tuberculosis in Africa, and *M. microti* causes disease in rodents. There are other species in the *Mycobacteria* genus known as *Mycobacteria* other than TB or MOTT. *Mycobacterium avium* complex is the most common.

*Mycobacteria* are slow-growing bacteria that are distinguishable by the fact that their cell walls are resistant to acid, thus the term acid-fast bacilli or AFB.

### **Differential Diagnosis:**

The differential diagnosis for pulmonary TB include lung cancer, community acquired pneumonia, lung abscess, and coccidioidomycosis.

### **Laboratory identification:**

Detection of acid-fast bacilli (AFB) in stained smears examined microscopically may provide the first bacteriologic clue of tuberculosis. Smear examination is an easy and quick procedure; results should be available within 24 hours of specimen collection. However, smear examination permits only the presumptive diagnosis of tuberculosis because the AFB in a smear may be *mycobacteria* other than *M. tuberculosis*. Furthermore, many tuberculosis patients have negative AFB smears.

Laboratory confirmation of TB infection is generally accomplished via culture and nucleic acid testing. Culture is highly sensitive and specific, however the organisms are slow to grow and isolation and identification can take weeks. Nucleic acid amplification can be performed directly on smears and, if positive, can reduce the time to confirmation to hours.

For all patients, the initial *M. tuberculosis* isolate should be tested for drug resistance. Drug susceptibility patterns should be repeated for patients who do not respond adequately or who have positive culture results despite two months of therapy.

### **Treatment:**

The typical treatment regimen includes isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB). Clinicians should consult with an infectious disease specialist or pulmonologist for dosage and duration.

The Centers for disease Control and Prevention and the American Thoracic Society have also issued a joint statement on the treatment of tuberculosis:

#### **American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of Tuberculosis**

**Am J. Respir Crit Care Med**

**Vol 167. pp 603-662, 2003**

<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm>

Adequate patient support ensuring that drugs are taken as prescribed, including directly observed therapy, is highly effective in achieving cure and is recommended for the treatment of tuberculosis disease worldwide.

Multidrug-resistant tuberculosis (MDR TB), which is defined as tuberculosis that is resistant to at least isoniazid and rifampin, presents difficult treatment problems. Treatment must be individualized and based on the patient's medication history and susceptibility studies.

An increasing concern is TB that is highly resistant to antibiotic therapy. This is known as extensively drug resistant TB (or XDR TB). XDR TB is resistant to the two primary antibiotics (INH and RIF), and to a secondary antibiotic class (fluoroquinolones) as well as to at least one of three injectable drugs (amikacin, kanamycin, or capreomycin.)

### **Case fatality:**

Worldwide, TB remains one of the deadliest diseases. One-third of the world's population, almost two billion people, is infected with *M. tuberculosis*. The World Health Organization (WHO) estimates 8 million people develop TB disease and 2 million die from TB each year, accounting for 7% of all deaths in the world and more than 25% of preventable deaths. Death rates in the U.S. are significantly lower, only about 4% of individuals with active disease die from TB.

### **Reservoir:**

Humans are the most common source of infection, but other mammals have been known to harbor the organism (e.g., monkeys, dogs). In some areas, diseased cattle, badgers, and swine are also infected. Human infection with *M. bovis*, the bovine tubercle bacillus, is still a problem in areas where the disease in cattle has not been controlled and where milk and milk products are consumed raw.

### **Transmission:**

TB is transmitted from person to person through the air by droplet nuclei (small particles 1–5 micrometers in size), generated by persons with infectious TB. Droplet nuclei are

produced when persons with pulmonary or laryngeal TB cough, sneeze, speak, or sing. Droplet nuclei may be produced by procedures, such as sputum induction, bronchoscopy, suctioning, or vigorous wound irrigation that produce aerosols. Except for rare circumstances, persons with TB disease outside the lungs (extrapulmonary) are not infectious. Infection occurs when persons have prolonged or repeated close exposure to an infectious person, with shared air space, and they inhale the organisms.

### **Susceptibility:**

The risk of infection with the tubercle bacillus is directly related to the degree of exposure and does not appear related to genetic or other host factors. The first 12-24 months after infection constitute the most hazardous period for the development of clinical disease. The risk of developing disease is highest in children under three, lowest in later childhood, and high again among young adults, the very old and the immunosuppressed. Population groups not previously touched by tuberculosis appear to have greater susceptibility to new infection and disease. Reactivation of long-latent infections accounts for a large proportion of tuberculosis disease cases in older people. For infected persons, susceptibility to tuberculosis disease is markedly increased by HIV infection and other forms of immunosuppression, and among the underweight or undernourished, people with a debilitating disorder (e.g. chronic renal failure, some forms of cancer, silicosis, diabetes or gastrectomy), or substance users/abusers.

### **Incubation period:**

The time from initial infection to a positive reaction using either the Mantoux tuberculin skin test (TST) method or an FDA approved in-vitro serologic test occurs between 2–12 weeks. Approximately 10% of individuals who acquire LTBI and who do not take a course of preventive treatment will develop active TB disease. While the risk of progression to TB disease is greatest within the first two years after infection, latent infection may persist for a lifetime. HIV infection and other cell-mediated conditions that impair immunity increase the risk and shorten the interval from infection to the development of TB disease. The risk of progression for persons co-infected with TB and HIV is 7–10% per year versus a lifetime risk of 5–10% otherwise. The risk of developing TB is also greater for children under two years of age. A positive tuberculin skin test usually persists, regardless of treatment.

### **Period of communicability:**

Only adults with TB of the lungs or other parts of the respiratory tract are usually infectious. Factors affecting the degree of infectiousness include: the number of bacilli expelled into the air, virulence of the organism, adequacy of ventilation, exposure of bacilli to sun or ultraviolet radiation, and opportunities for aerosolization through coughing, sneezing, talking or singing, or during procedures. Effective treatment usually eliminates communicability within 2–4 weeks, even though TB bacteria may still be seen in or may grow from expectorated sputum. Virulence of the TB organism and susceptibility of the host also play a role in transmission. Medical conditions such as HIV infection, other immune system compromise, or malnutrition increase one's risk of being infected, if exposed.

Although transmission has been known to occur, children are generally not infectious.

### **Epidemiology:**

Since 1953, the U.S. TB case rate has declined tenfold to a rate of 4.8/100,000 population in 2004. The decrease in the percent change of the annual case rate has slowed, from an annual average of 5.6% for 1993 through 2002 to an average of 3.1% for 2003 through 2005. The 14, 097 TB cases reported to CDC for 2005 represented a 2.9% decrease from 2004 and a 47% decrease from 1992, when the number of cases and the case rate peaked during a resurgence in the United States. The resurgence of TB in the U.S. in the late 1980s and early 1990s was associated with the emergence of multi-drug resistant (MDR) TB and the HIV/AIDS epidemic. The overall decrease in cases in the last decade primarily reflects a decrease in the number of cases among U.S.-born persons, with substantial declines in all age groups.

In the United States, there are approximately 14,000 reported cases annually with about 600 deaths. In Utah, 30-40 cases are reported annually. In Utah, 68% of TB cases were non-U.S.-born (5 year average, 2002-2006).

## **PUBLIC HEALTH CONTROL MEASURES**

### **Public health responsibility:**

- Investigate all suspect cases of disease and fill out and submit appropriate disease investigation forms.
- Assure that therapy is provided and taken to reduce the occurrence of drug resistance.
- Provide education to the general public, clinicians, and first responders regarding disease transmission and prevention.
- Identify clusters or outbreaks of this disease.
- Identify sources of exposure and stop further transmission.

### **Prevention:**

There are few preventive measures that individuals can take to protect themselves from this disease.

Public health plays a major role in preventing new cases among uninfected individuals. It is essential that public health promptly identify, diagnose, and treat potentially infectious patients with tuberculosis disease. The best prevention for TB disease is to effectively control all diseased individuals and prevent further transmission.

### **Chemoprophylaxis:**

Individuals with LTBI may receive INH prophylaxis (possibly with pyridoxine or rifampin). The decision to test represents a decision to treat to completion of therapy.

The following groups should receive chemoprophylaxis regardless of age:

- $\geq 5$ mm reaction: HIV+; close contact of TB case; fibrosis on chest X ray; or immunosuppressed
- $\geq 10$  mm reaction: recent immigrant; injecting drug user; resident/employee of prison, jail, nursing home, hospital, shelter; diabetes mellitus, renal failure, leukemia/lymphoma, weight loss, gastrectomy; child < 4years old
- Anyone with  $\geq 10$ mm increase in induration within 2 years or with  $\geq 15$  mm reaction.

#### [Information on treatment](#)

### **Vaccine:**

Vaccination with the bacilli Calmette-Guerin (BCG) is not generally recommended in the United States because of the low risk of infection with *M. tuberculosis*, the variable effectiveness of the BCG vaccine against pulmonary tuberculosis, and the vaccine's interference with the ability to determine tuberculin reactivity using the Mantoux tuberculin skin test.

Tuberculin skin testing is not contraindicated for persons who have been vaccinated with BCG, and the skin-test results of such persons are used to support or exclude the diagnosis of *M. tuberculosis* infection. A diagnosis of *M. tuberculosis* infection and the use of treatment for infection should be considered for any BCG-vaccinated person who has a tuberculin skin-test reaction of  $\geq 10$  mm of induration. Treatment for infection should be considered for BCG-vaccinated persons who are infected with HIV and who are at risk for *M. tuberculosis* infection if they have a tuberculin skin-test reaction of  $\geq 5$  mm induration.

The in-vitro serologic testing method, QuantiFERON – TB Gold, is not contraindicated for persons who have been vaccinated with BCG, as the proteins used in this test are absent from all BCG vaccine strains.

### **Isolation and quarantine requirements:**

**Isolation:** In general, patients are isolated at home until they have completed at least 2 weeks of adequate therapy, show clinical improvement, and are smear negative. Public health pursues involuntary isolation orders for non-compliant patients.

**Hospital:** AFB precautions including placement in a negative pressure room, appropriate signage, entry limited to those wearing N-95 respirators, and masking patients if they have to leave their room.

**Quarantine:** None

## **CASE INVESTIGATION**

### **Reporting:**

Tuberculosis is an immediately reportable disease. Due to the lengthy period of time required for confirmation of illness, providers and laboratories are urged to report suspect cases of disease (i.e. individuals with positive AFB smears from sputum) to public health.

## **Case definition:**

### **Tuberculosis (1996):**

#### **Clinical Description**

A chronic bacterial infection caused by *Mycobacterium tuberculosis*, characterized pathologically by the formation of granulomas. The most common site of infection is the lung, but other organs may be involved.

#### **Clinical Case Definition**

A case that meets the following criteria:

- A positive tuberculin skin test or FDA approved in-vitro serological test
- Other signs and symptoms compatible with tuberculosis (e.g., an abnormal, unstable [i.e., worsening or improving] chest radiographs, or clinical evidence of current disease)
- Treatment with two or more antituberculosis medications
- Completed diagnostic evaluation

#### **Laboratory Criteria**

- Isolation of *M. tuberculosis* from a clinical specimen\* or
- Demonstration of *M. tuberculosis* from a clinical specimen by nucleic acid amplification test,\*\* or
- Demonstration of acid-fast bacilli in a clinical specimen when a culture has not been or cannot be obtained

#### **Case Classification**

*Confirmed:* a case that meets the clinical case definition or is laboratory confirmed.

#### **Comment**

A case should not be counted twice within any consecutive 12-month period. However, cases in which the patients had previously had verified disease should be reported again if the patients were discharged from treatment. Cases also should be reported again if patients were lost to supervision for greater than 12 months and disease can be verified again. Mycobacterial diseases other than those caused by *M. tuberculosis* complex should not be counted in tuberculosis morbidity statistics unless there is concurrent tuberculosis.

\*Use of rapid identification techniques for *M. tuberculosis* (e.g., DNA probes and mycolic acids high-pressure liquid chromatography performed on a culture from a clinical specimen) are acceptable under this criterion.

\*\*Nucleic acid amplification (NAA) tests must be accompanied by culture for mycobacteria species. However, for surveillance purposes, CDC will accept results obtained from NAA tests approved by the Food and Drug Administration (FDA) and used according to the approved product

labeling on the package insert. Current FDA-approved NAA tests are only approved for smear-positive respiratory specimens.

## **Case Investigation Process:**

Investigators should:

- Perform medical record review
- Determine whether case is latent or active
- Determine whether case is receiving appropriate antibiotic therapy
- Interview the client (TB case interview)
- Identify case contacts
- Perform risk assessment for MTB transmission
- Manage case contacts
- Field investigation

## **Outbreaks:**

Definitions for TB outbreak are relative to the local context. Outbreak cases can be distinguished from other cases only when certain associations in time, location, patient characteristics, or *Mycobacterium tuberculosis* attributes (e.g., drug resistance or genotype) become apparent. In low-incidence jurisdictions, any temporal cluster of cases is suspicious for an outbreak. A working definition for a potential "TB outbreak" is helpful for planning and response and may include any of the following six criteria:

Criteria based on surveillance and epidemiology:

- An increase has occurred above the expected number of TB cases
- During a contact investigation (CI), two or more contacts are identified as having TB disease, regardless of their assigned priority, (i.e., high-, medium-, or low-priority)
- Any two or more cases occurring within one year of each other are discovered to be linked, and the linkage is established outside of a CI (e.g., two patients who received a diagnosis of TB disease outside of a CI are found to work in the same office and only one or neither of the persons was listed as a contact to the other)
- A genotyping cluster leads to discovery of one or more verified transmission links which were missed during a CI within the prior two years

Criteria based on program resources:

- Transmission is continuing despite adequate control efforts by the TB control program
- CI associated with increased cases requires additional outside help

## **Identification of case contacts:**

The contact investigation is an integral part of the TB Control Program and one of the best ways to find people who have active tuberculosis disease. The purpose of the

investigation is to find contacts who have active tuberculosis so that they can be given treatment and further transmission can be stopped; have latent tuberculosis infection (LTBI) so they can be given treatment; and, are at high risk of developing active tuberculosis and therefore require treatment until latent tuberculosis infection can be excluded. Each local health department is responsible for ensuring that a complete and timely contact investigation is done for tuberculosis cases and highly suspect tuberculosis reported in its area.

For specific information relating to the contact investigation please refer to:

**Centers for Disease Control and Prevention, Guidelines for the investigation of contacts for persons with infectious tuberculosis; recommendations from the National Tuberculosis Controllers Association and CDC, and Guidelines for using the QuantiFERON-TB Gold test for detecting *Mycobacterium tuberculosis* infection, United States. MMWR 2005;54 (No. RR-15).**

Skin testing or the use of an FDA approved in-vitro serologic testing (e.g. QuantiFERON) method is used for all members of the household and other close contacts. If negative, a repeat test should be repeated 10-12 weeks after the last exposure. Chest X-rays should be obtained for all individuals found to be infected.

### **Case contact management:**

See the [treatment](#) and [chemoprophylaxis](#) sections for more information on treating latent infection.

A decision to test is a decision to treat to completion. In order for a contact investigation to be complete, all eligible contacts must complete therapy. Attention should be focused on treating contacts who are assigned high or medium priority. Priority ranking is determined by the characteristics of individual contacts and the features of the exposure. Contact investigations of persons with AFB smear or culture-positive sputum and cavitary tuberculosis are assigned the highest priority.

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Am J. Respir Crit Care Med

Vol 167. pp 603-662, 2003

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